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(54) Title: METHOD FOR TREATMENT OF ACUTE AND CHRONIC PAINFUL ARTHROPATHIC CONDITIONS IN HUMAN AND OTHER MAMMALS

(57) Abstract

A method for treating inflammatory conditions in mammals, including humans and horses, by administering to said mammal an effective amount of sodium chondroitin sulfate C, sodium chondroitin sulfate D, or mixtures thereof, which are essentially free of endotoxin. Optionally, sodium chondroitin sulfate C, sodium chondroitin sulfate D, or mixture thereof may be blended up to 40 wt % with sodium chondroitin sulfates derived from bovine trachea and bovine nasal septum. The preparations may be administered parenterally, intramuscularly, or transdermally.

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METHOD FOR TREATMENT OF ACUTE AND CHRONIC PAINFUL ARTHROPATHIC CONDITIONS IN HUMAN AND OTHER MAMMALS

FIELD OF THE INVENTION

The present invention is directed toward a method for treatment or prophylaxis of painful conditions, especially pain associated with degenerative conditions of both hard and soft tissues, by the administration of a pain relieving effective dose of an angiogenesis inhibiting effective amount of sodium chondroitin sulfates to animals of mammalian species, including humans, in a safe and efficient manner.

BACKGROUND OF THE INVENTION

As used herein, the term "arthritic disease" refers to any disease state characterized by significant joint inflammation associated with secondary pain. "SCS" as utilized herein in the specification and claims is the acronym for sodium chondroitin sulfate. The product, SCS is a purified extract of shark cartilage.

The applicant is aware of the following prior art which pertains to the subject matter of this application.

INFLAMMATORY JOINT DISEASES

A major consequence of chronic inflammatory joint disease (rheumatoid arthritis) and degenerative arthritis (osteoarthritis or osteoarthrosis) is loss of function of those effected joints. Osteoarthrosis usually has an insidious onset of pain, stiffness and reduced range of movement. It commonly affects one or only a small number of joints. Joint laxity develops with locking and aberration. Most often effected are the joints which have been used the most or previously effected by trauma or inflammatory processes. Such joints suffer the greatest damage. Thus, the weight-bearing joints of the hips and knees, the lumbar spine and first carpometacarpal joints are common victims of the disease.

The essential features of rheumatoid arthritis are cyclic pain and swelling of several joints with morning stiffness continuing for several weeks. It tends to affect the peripheral small joints symmetrically.

Other common inflammatory arthropathies include alkylosing spondylitis, psoriatic arthropathy, septic (suppurative) arthritis, Reiter's disease and gouty arthritis. Other

traumatic and non-traumatic joint injuries include synovitis, capsulitis and the like.

The loss of function is due to destruction of the major structural components of the joint, cartilage and bone, and subsequent loss of the proper joint anatomy. As a consequence of chronic disease, joint destruction ensues and can lead to irreversible and permanent damage to the joint and loss of function. Destruction of architecture of the joint may be mediated by angiogenesis.

ANGIOGENESIS

Angiogenesis is the development of a network of blood vessels which typically would lead to a vascular bed capable of sustaining viable tissue. It is characterized by the directed growth of new capillaries toward a specific stimulus, many of which have been proposed. Angiogenesis is a necessary step. It has been implicated to play an important role in the pathophysiology (the establishment and development) of certain inflammatory conditions. In osteoarthritis, for instance, it is involved in the reinitiation of cartilage growth and mineralization. Also, the vascular proliferation appears to be important in the pathogenesis of rheumatoid arthritis. Semble et al., J. Rheumat. 12: 237, 1985. Thus, the inhibition of a angiogenesis is a prerequisite objective to control/alleviate inflammatory conditions.

ANTI-INFLAMMATORY DRUGS

It is apparent from the discussion above that the inflammatory diseases of the joints cause an extremely high level of discomfort and pain and in many instances the results are crippling. The requirement for treatment is unquestioned and the treatment is in many cases continuous as none of commercially available drugs for treatments of these diseases is significantly effective in achieving true remission of the disease in most individuals affected by these diseases. Thus, the disease is, generally speaking, incurable.

The commonly used anti-inflammatory drugs which are sometimes administered with other analgesics, have been shown to have significant drawbacks including exhibiting several (and

often severe) side effects, for instance, faecal blood loss (anti-prostaglandins), hypertension (glucocorticoid), bone marrow depression (immunosuppressants) or intestinal ulceration (NSAIDs - non-steroid anti-inflammatory drugs). Obviously, the drugs that would alleviate inflammatory conditions by inhibiting angiogenesis are of great interest.

ANGIOGENESIS INHIBITORS

Several naturally-occurring angiogenesis inhibitors have been found. For instance, Research Resource Reporter, page 7, December 1981, reports the isolation of factor from cartilage which slows tumor growth and also reports similar factors from other tissues. However, all these factors appear to be proteins having molecular weights in the range between 3,500 and 25,000 Daltons. Also, J. Folkman, et al., Science, 221: 719, 1983, describes the angiogenesis inhibitory effects of heparin and heparin fragments.

Moreover, at present all of identified candidate drugs exhibit severe host toxicity. Maione et al., Trends Pharmacol. Sci, 11, 457, 1990.

It is apparent that a composition which would inhibit the action of angiogenesis factor in promoting the development of blood vessels, would have an adverse effect upon the growth of tumors, on the development of the psoriatic lesion, on development of retinopathy or rheumatoid arthritis.

CHONDROITIN SULFATE PREPARATIONS AS THERAPEUTIC AGENTS

The use of chondroitin sulfate preparations in treatment of and as preventive therapy for a variety of diseases has been previously reported.

The use of these drugs in the treatment of cardiovascular diseases including myocardial infractions, acute coronary insufficiency and acute myocardial ischemia are described in U.S. Pat. Nos. 3,895,106 and 3,894,107 to Morrison.

U.S. Patent No. 4,640,912 to Hausman describes the use of chondroitin sulfate preparations in the treatment and reduction of incidence of pathological conditions ranging from cancer, bacterial infections, trauma, irritation or damage to the linings of the renal pelvis, ureter, urethra and bladder caused

by placement of foreign objects, tubes or instruments into the renal pelvis, ureter, urethra and bladder or kidney.

Among the most pertinent prior art known to applicant is U.S. Pat. No. 4,971,955 issued November 20, 1990 to Soll et al. The patent relates to the utilization of chondroitin sulfate as a protective agent prior to and/or during anticipated trauma and to promote separation of tissue planes during surgical intrusions. Soll et al. disclose that chondroitin sulfates are useful in alleviating aseptic joint inflammation (i.e. microorganism-free infection) of the large joints and preventing further degeneration of the cartilage through protection of cells in the joint cavity and through lubrication of the joint surfaces of four-legged animals such as horses. Chondroitin sulfate isolated from shark cartilage has been found particularly useful in anterior segment surgery. The mode of action of chondroitin sulfates in their passive and active role has been discussed in some detail in this patent. Patentees further disclose that chondroitin sulfates may limit or even eliminate the activities of accidental septic infections (i.e. caused by microbial invasion). Since chondroitin sulfates are viscous, they restrict the movement and the flow of inflammatory products such as proteins and large molecules.

DIMETHYL SULFOXIDE

The use of dimethyl sulfoxide as an agent for enhanced tissue penetration of other substances is known in the art. It is, for example, described in great detail in U.S. Pat. No. 4,296, 104, No., 3,551,554, No 3.711,606 and No. 3,743,727.

Cartilage is one of few avascular tissues in the body. The notion that a factor (molecule(s)) endowed with angiogenesis inhibitor activity may be present in mammalian cartilages is not new. Several fractions having such activity have been identified in and prepared from natural sources, including calf and shark. The latter became an especially attractive source since it has been observed that elasmobranchs such as sharks, in contrast to mammals and even bony fish and

amphibians, rarely exhibit neoplasm. See Guenther et al., Biochim. Biophys. Acta, 372, 321; 1974.

Leur has described the angiogenesis inhibitory activity of shark cartilage (Federation Proceedings, September 1986) but failed to teach or suggest analgesic properties, which are especially useful in the treatment of inflammations in hard and soft tissue in mammals.

In an article published in Science, 221, 1185;1983, Langer and co-workers have reported the presence of the angiogenesis inhibitory activity in both calf and shark cartilage and have described the high extraction of this inhibitor from shark as opposed to calf cartilage. More specifically, the authors have noted that one weight unit of shark cartilage extract inhibits roughly one thousand times stronger vascular growth toward solid tumors than the same amount of extract from calf cartilage. Yet, they have failed to identify the nature of the inhibitor molecule. Moreover, Langer and co-workers have observed that the fractions having increased collagenase specific activity are practically free of significant angiogenesis inhibitory activity. The only utility which is disclosed refers to proposed antitumor studies.

In a more recent paper from the same laboratory relating to cartilage-derived neovascularization inhibitor (CDI) it has been reported that chondroitin sulfate A does not inhibit angiogenesis in vivo. See Moses et al., Science, 248: 1408,1990. CDI molecule is a 28 amino acid peptide extracted from calf scapular cartilage. This reference apparently suggests that there may be subtle differences in the amino acid sequences from species to species, however the presence of the angiogenesis inhibitor and its physiological activity are essentially identical., i.e. prevention of neovascularization in otherwise avascular cartilage. Bovine and other mammalian sources yield predominantly chondroitin sulfate A (see U.S. Patent No. 3,895,106 to Morrison; see also U.S. Patent No. 4,302,577 to Rucker). Therefore, it is apparent that CDI molecule(s) taught by this reference are not associated with chondroitin sulfates. In contrast to this communication, the

applicant has found that the sodium chondroitin sulfate preparations used in the claimed method inhibit both angiogenesis and collagenase activity. Heretofore, it has not been recognized in the art of pharmacology and medicine that collagenase and angiogenesis inhibitory activity-rich preparations of sodium chondroitin sulfate derived from shark cartilage extract may have utility in the treatment and relief of pain, especially pain associated with the various forms of inflammations including the inflammations of hard and soft tissue.

Similarly, Oikawa et al., (Canc. Lett, 51, 181: 1990) reported that their heat resistant fractions in the molecular weight range between 10^3 and 10^4 of Japanese basking shark cartilage have angiogenesis -inhibitory activity.

SUMMARY OF THE INVENTION

The present invention relates to a method useful for effectively treating, relieving and preventing both acute and chronic pain, especially such pain associated with inflammation of both hard and soft tissues in animals of mammalian species, including humans in an efficient and patient-friendly manner. The methods are very powerful and effectively inhibit both angiogenesis and collagenase activity. The method entails administering a sterile and endotoxin free pharmacologically effective amount of sodium chondroitin sulfate derived from shark cartilage extract, preferably via systemic routes of administration such as, for example, parenteral routes. Sodium chondroitin sulfate is a sodium salt of chondroitin sulfate C, sodium salt of chondroitin sulfate D (sodium salt of chondroitin polysulfate) or mixtures thereof. Sodium chondroitin sulfates from shark cartilage may be blended with sodium chondroitin sulfates from a non-shark source, for example, a mixture of at least 60 wt % of sodium chondroitin sulfate derived from shark cartilage and up to 40 wt % of sodium chondroitin sulfates derived from a non-shark source.

Because of its long duration of action, the claimed method is particularly well-suited for both systemic and local treatment. Thus, apart from systemic routes of administration,

the method of this invention may be used for treating individuals in need of such pain relieving treatment locally at a disease site, for example, via intra-articular injections or transdermal applications.

Using the methods of the invention, substantial improvement can be obtained in the efficacy of the treatment since the utilized mixture of sodium chondroitin sulfates, in terms of both angiogenesis inhibitory activity and collagenase inhibitor activity, is found to be up to 1000 times more potent on a milligram basis than the prior art compositions.

This invention also provides a method of transdermal topical patch drug delivery for the treatment both locally and systemically of painful conditions of soft and hard tissues. This method entails administering a pharmacologically effective amount of sodium chondroitin sulfate derived from shark cartilage and dimethyl sulfoxide (DMSO) to enhance tissue penetration. Sodium chondroitin sulfate (SCS) as used herein is a sodium salt of chondroitin sulfate C, sodium salt of chondroitin sulfate D (sodium salt of chondroitin polysulfate) or mixtures thereof. A blend of sodium chondroitin sulfates from shark cartilage and sodium chondroitin sulfates from a non-shark source, for example, at least 60 % by weight of SCS and up to 40 % by weight of non-shark SCS, preferably a mixture of from about 65 to about 95 wt % of sodium chondroitin sulfate C derived from shark cartilage and from about 5 to 35 wt % of sodium chondroitin sulfates derived from a non-shark source may be used to practice this invention.

The treatment of painful conditions which often occur in conjunction with angiogenesis, such as bursitis or tendinitis, is also comprehended by the present invention.

The SCS preparation used in the present invention is a heterogeneous glycosaminoglycan preparation with peptide content. The peptide is linked to the chondroitin sulfate and to the chondroitin polysulfate in specific linkage regions. See Seno, J.Biochem., 83, 953-6: 1978; see also Akiyama et al, Biochem. Biophys. Acta, 674, 289-96: 1981). When derived from natural sources, the peptide is chemically bound to the

chondroitin sulfate molecule. Also, it is known that even the highly purified preparations of the chondroitin sulfates contain residual proteins (up to 17 wt %) which appears to be resistant to the treatment with various types of proteases. In terms of the purity, the composition of the instant invention is sterile and free of endotoxin, and is pharmaceutically acceptable as an administrable drug preparation via parenteral routes.

These and other advantages and objects of the invention will become apparent from the following more detailed description of this invention.

DETAILED DESCRIPTION OF THE INVENTION

According to Soll et al chondroitin sulfate is effective in their invention at all molecular weights, i.e in order of about 50,000 to 100,000 Daltons, depending on the source, if administered topically or directly to the aggrieved cells.

It has now been found that the blend of high molecular weight, analgesic specific fractions of the sodium salt of chondroitin sulfate (i.e., sodium chondroitin sulfate C, sodium sulfate D, or mixtures thereof) which is associated with both angiogenesis and collagenase inhibitors and derived from both non-shark and shark cartilage is active pharmacologically when administered parenterally to human and other mammals including for example, horses and dogs. The blend contains at least 60 wt %, preferably from about 65 to 95 wt %, and more preferably about 95 wt % of shark cartilage sodium chondroitin sulfates and up to 40 wt %, preferably from 5 to 35 wt % of sodium chondroitin sulfates derived from a cartilage of non-shark-origin. When non-shark cartilage is used, it is preferably mammalian cartilage, and more preferably bovine cartilage. Preferably, the non-shark source is selected from bovine trachea and bovine nasal septa. A highly purified chemical grade blend of shark sodium chondroitin sulfate (70 wt %) and bovine sodium chondroitin sulfates (30 wt %) is now commercially available.

This blend of SCSs is most useful for treating both acute and chronic painful conditions of both hard and soft tissues where an inappropriate development of capillary vessels leads to further progression of degenerative conditions (i.e., degenerative joint diseases, rheumatic diseases, etc.). The representative examples of soft tissue injury include sprains and strains of ligaments, tendons, and muscles. Degenerative joint disease is an example of a hard tissue injury.

It has further been found that a high molecular weight fraction of sodium chondroitin sulfates (SCS) derived from shark cartilage, preferably from shark fin, is superior to lower molecular weight sodium chondroitin sulfates derived from shark skin and vertebral column and from mammalian cartilage in terms of both analgesic and anti-angiogenesis properties.

Shark fin derived SCS is predominantly sodium chondroitin sulfate C (SCS-C) or sodium chondroitin sulfate D (SCS-D) (also known as sodium chondroitin polysulfate) which is a polysulfated form of sodium chondroitin sulfate C. It is sodium chondroitin sulfates C and D, which exhibit the analgesic effect of the present method. The molecular weights of chondroitin sulfates extracted from shark fin cartilages which are effective in the present invention ranges from 18,000 to 104,000 Daltons. Preferably, the fractions comprising chondroitin sulfates having a molecular weight of at least 40,000 are used to practice the invention. The fractions having a molecular weight in the range from 40,000 to 55,000 Daltons are especially preferred. It has been found that the higher molecular weight coincides with a higher viscosity and a more concentrated presence of angiogenesis inhibitor peptide and a greater number of SCS molecules per weight unit of raw material. It has been further found that the preparation in the higher molecular weight ranges demonstrates enhanced collagenase inhibitor activity. SCS-C derived from shark vertebral column and shark skin have molecular weights in the range of 28,000 to 35,000. From the pharmacological point of view, these differences in molecular weights make the higher molecular weight fractions more desirable, although the lower

weight SCS preparations can also be utilized for the therapeutic indications previously described.

The exact mechanism of action has not been established yet. However, to explain the beneficial effects of the claimed composition it is proposed that the composition:

a) is a potent inhibitor of collagenase and proteolytic enzymes;

b) protects cellular membranes from enzymatic degradation;

c) stimulates chondrocytes and synoviocytes to produce high molecular weight sulfated and non-sulfates glycosaminoglycans;

d) is a powerful scavenger of oxygen-derived free radicals;

e) causes a sharp decline of proinflammatory mediators , i.e., PGE-2, LTB-4, LTC-4, and the like, in inflammatory exudates;

f) is a potent angiogenesis factor inhibitor which suppresses the hyperproliferation and migration of capillary endothelial cells in and around damaged cartilage and subchondral bone; incidentally in the normal state these structures are essentially avascular and they become abnormally hypervascularized as degenerative arthritic conditions progress.

It should be noted that the process of neovascularization may play a major role in the hyperproliferation and calcification of cellular and non-cellular components within the affected tissues of individuals with painful degenerative and non-degenerative inflammatory conditions.

A powdered form of a highly purified chemical grade preparation of shark cartilage is commercially available. One of the identified manufacturers of the highly purified chemical grade preparation of shark cartilage is Calbiochem Behring Corp., LaJolla, California. This commercial preparation has been used in various chemical processes such as a process for

the selective extracorporeal precipitation of low-density lipoprotein described in U.S. Patent 4,908,354 to Seidel et al. Also, an extract containing 99.5 % of a mixture of sodium chondroitin sulfate C and sodium chondroitin sulfate D, and a highly purified chemical grade blend of shark sodium chondroitin sulfates (70 wt %) and bovine sodium chondroitin sulfates (30 wt %) are commercially available.

A stock solution of ten percent weight/volume is prepared by dissolving the shark cartilage extract sodium chondroitin sulfates in sterile water for injection USP. The stock solution is then sterilized initially by filtration through a series of suitable microporous filters. Preferably, these membranes have an absolute pore rating in the range from about 0.22 micrometer to about 0.5 micrometer. Most preferably, 0.22 micron disk filters manufactured by and commercially available from Millipore Corporation, Bedford, MA are used. The sterile solution is collected into a sterile evacuated container, preferably glass.

It has been also found that it is imperative to remove all traces of endotoxin that may be present, even in SCS products manufactured as pharmaceutical grade i.e., sterile and pyrogen free. It should be noted that even commercially available product designated "endotoxin free" still may contain up to 0.5 μg/ml of endotoxin, as allowed by the FDA standards upon meeting the standards of the pyrogen-free test (endotoxin test). Sterile solutions of sodium chondroitin sulfates that contain pyrogens and/or endotoxins are not only worthless as analgesic agents parenterally, but are harmful and actually make painful conditions much worse due to the "pyrogen reaction." Severe and local painful reactions occur at sites of injection and generalized whole body soreness with weakness, malaise, muscle and joint pain with joint inflammation, fever, chills, decrease in blood pressure, nausea and vomiting are some of the harmful effects of contaminated solutions of sodium chondroitin sulfates that are merely "sterile." Shark cartilage extracts contain harmful pyrogens and endotoxins as well as other proteins which are capable of causing severe and

even fatal allergic/hypersensitivity reactions when used for injections. Accordingly, remaining endotoxins are removed by filtering the sterile stock solution through endotoxin removing filters.

It has been found by the present inventor that by utilizing a series of endotoxin removing filters, preferably Pall Posidyne filters, one is able to ultrapurify the commercially available product from residual endotoxin contamination. The inventor has further found that a minimum of five (5) filters in succession is necessary to obtain suitable preparations. The resultant solution is both sterile and endotoxin-free.

Nylon microporous filter membranes which may be used in the endotoxin removal step are commercially available. One of suitable filter membrane is manufactured by the cocasting process and available from Pall Corporation, Biosupport Division, of Glen Cove, New York, under the trademark SCF or the trademark Set SAVER, or the trademark N66 Posidyne. A matrix of Nylon 66 is modified and functionalized with a high density of positively charged groups on its surface, typically by the addition of quaternary amine groups. According to the manufacturer, a high concentration of these cationic functional groups at the pore surface of the material displays a little variation in a positive zeta potential in both acidic and basic solutions over a wide pH range and is preferably designed to remove a variety of substances including endotoxin, i.e., toxins produced as a result of bacterial growth or decomposition. See Degen, et al., U.S. Patent 4,702,804.

The foregoing filter materials are illustrative of suitable positively charged matrices that may be used in preparing stock solution for use in the pharmaceutical composition of this invention. Any suitable microporous polymeric membrane may be used. The criteria for selecting the filter include, for example, the requisite porosity, ability to withstand sterilization techniques, including gamma ray radiation, and charge capability for effectively removing endotoxin.

The stock solution may be passed through one or more filters. Preferably, a series of at least five 0.22 micron Pall brand Posidyne™ endotoxin removing filters are used to practice this invention.

FORMULATION AND ADMINISTRATION

Compositions containing the active analgesic fractions for treatment of pain may be internally administered to a living animal body in any one of various ways, for example, parenterally in the form of sterile solutions or suspensions and in some cases intravenously in the form of sterile solutions. In forming the compositions, the active ingredient, i.e. sodium chondroitin sulfate C, D or mixtures thereof is incorporated in a suitable carrier, illustratively a pharmaceutical carrier, i.e., water, saline, and the like.

The compositions of the invention may be produced by any of the following general methods.

In a first embodiment, the compositions of the invention are prepared by simply mixing the endotoxin-free fractions as described above with known pharmaceutically acceptable carrier(s) by any art-known method.

In a second embodiment, the compositions of the present invention are prepared by admixing DMSO with the endotoxin-free composition. According to the invention, pharmaceutical compositions containing both SCS and DMSO have greater effectiveness than could be predicted by combining (in additive fashion) the known or theoretical effectiveness of the individual agents. It has been found, for example, that the addition of dimethyl sulfoxide (DMSO) in amounts of from about 50 to 99 % by weight, and preferably from about 90 to 99 weight percent, to sodium chondroitin sulfates composition will significantly enhance the penetration of the SCS into the blood stream. Additional information concerning the effectiveness of DMSO in transporting large molecules (high-molecular weight molecules) through the intact skin may be found, for example, in Remington's Pharmaceutical Sciences, 15th Edition.

Advantageously, the compositions are formulated as dosage units, each unit being adapted to supply a fixed dose of active

ingredient(s). Unit ampules and prefilled syringes are examples of preferred dosage forms, however, the composition may be offered in multiple-dosage containers and the like. Each unit dose will contain an amount of SCS effective to inhibit angiogenesis. It is only necessary that the active ingredient constitutes an effective amount, i.e., such that a suitable dosage will be consistent with the dosage form employed. The exact dosages, as well as daily dosages for the subject, may vary depending on whether the subject is human or animal and according to such factors as age, sex, extent of the disease, and so forth, but for instance in horses, usually a therapy is initiated by administering intramuscularly a one time loading dose of about 1,000 mg, followed 48-96 hours later with a maintenance dosage of about 500 mg (intramuscularly) every 48-96 hours, based on the individual response. The daily parenteral dosage for a sexually mature human subject is from 0.5 mg to 2.0 milligrams per kg of body weight, with from 0.5 to 1 milligram per kg of body weight being preferred per unit dose.

The SCS containing composition used herein is safe and efficacious in remission of painful inflammatory conditions and other painful conditions. Acute, subacute and chronic administration of the composition in horses revealed no signs or symptoms of toxicity even at dosages exceeding six times the recommended dose (up to 3,000 mg) administered for fourteen (14) weeks. Peak plasma levels of the composition are achieved within one to two hours following a single intramuscular injection, although there may be considerable individual variations. Plasma half-life and analgesic activity may reflect factors such as protein binding, organ uptake and concentration of the active agent in analgesic exudates.

The active agents of the invention may be combined with other pharmacologically active agents, or with buffers or the like for administration as long as the antagonistic effect is avoided. The proportions of these agents in the composition may vary widely.

The parenteral dosage forms may be injected by the subcutaneous, intramuscular, intravenous or intra-articular routes. For parenteral administration, the composition is administered in solution or suspension and its dosage may include any conventional injectable solutions together with pharmaceutically acceptable preservatives and buffers. For intramuscular injections it is preferred that the chondroitin sulfates are present at a final concentration of about 10 % (wt/vol) in a pharmaceutically acceptable vehicle. For intra-articular injections, the preferred concentrations of the chondroitin sulfates are in the range from about 10 to 25 % (wt/vol). Preferred daily dose levels in mammals would be up to 1 mg/kg of mammalian body weight.

The SCS-containing composition may also be provided in powder form which is redissolved before use in a suitable vehicle, for instance, sterile, endotoxin free water or saline.

Based on animal test results, it is clear that administering an effective dose of SCS alone or in combination with DMSO according to the present invention, is an effective method for reducing pain associated with inflammatory and other painful conditions.

Applicant has found that an inflammatory or other painful conditions may be successfully treated by applying to the skin a mixture of sodium chondroitin sulfate and dimethyl sulfoxide in amounts effective to ameliorate the inflammation when applied to an area of the skin proximate to the inflammation. More specifically, the method which utilizes a dimethyl sulfoxide-sodium chondroitin sulfate transdermal topical patch drug delivery system has been found to be effective for the treatment of painful inflammatory conditions of soft and hard tissues, both locally and systemically. The preferred form of the topical patch delivery system contains a mixture of sodium chondroitin sulfate(s) combined with dimethyl sulfoxide in a ratio of from about 1:1 to about 1:15 by weight. A more preferred form of the topical patch drug delivery system contains about 10 wt % of the mixture of sodium chondroitin

sulfate and about 90 wt % of DMSO. The patch is applied to a shaved, clean and non-irritated area of skin and changed every 96 hours. The contained mixture is slowly released and penetrates the skin to deliver both local and systemic medication. It is hypothesized that the ingredients act together to achieve a synergistic result more effective than can be obtained from both agents individually, and more effective than could be predicted from the mere addition of the known efficacies of the individual ingredients.

The method of the present invention provides effective symptomatic relief for individuals suffering from arthritic disease, pain associated inflammatory conditions, or other painful conditions. It is believed that in many instances, true remission of these diseases will be achieved.

EXAMPLE 1

TEST PROCEDURES FOR ASSESSING DEGREE OF LAMENESS IN EXPERIMENTAL ANIMALS

Thirty three standard bred racehorses suffering from various physical maladies, for instance, lameness due to various traumatic and non-traumatic inflammatory conditions including degenerative joint disease, tendinitis (bowed tendons), suspensory ligament desmitis, ligament strains and sprains, periostitis and sore muscles have been subjected to treatment with the composition of the present invention. All horses displayed soreness and or lameness prior to initial treatment with the composition of this invention. The degree of lameness was rated 0 to 3 with 0 being least severe and 3 being the most severe by the objective criteria.

Each of these horses was administered an initial loading dose of 1000 mg of a blend of about 70 wt % of sodium salt of chondroitin sulfate C derived from shark cartilage and about 30 wt % of sodium salt of chondroitin sulfates derived from bovine nasal septa/trachea via the intramuscular route. This preparation was purchased from SKK - Japan and further purified to remove endotoxin as previously described. The animals were

examined twenty-four (24) hours later and a response was evaluated.

A favorable response was based on a three (3) point improvement seen after 24 hours from the drug administration. Rating of the improvement was based on the degree of local signs and symptoms of pain, including local heat, swelling, tenderness and range of motion.

Twenty-eight (28) horses were judged to have had an excellent response from a single 1000 mg (10 ml) injection of a blend of about 70 wt % of sodium salt of chondroitin sulfate C derived from shark cartilage and about 30 wt % of sodium salt of chondroitin sulfates derived from bovine nasal septa/trachea. There was a marked reduction of symptoms so as to allow training or racing without soreness or lameness. Ninety-six (96) hours following the initial dose all thirty-three (33) horses were again treated with a single 500 mg intramuscular injection of the same preparation. 24 hours later all 33 horses were judged to have had a beneficial response. The degree of lameness was rated 0 to 3 with 0 being least severe and 3 being the most severe by the same objective criteria. Table 1 records the results of this experiment.

EXAMPLE 2

Forty lame race-horses were equally assigned to two treatment groups, i.e., Group I and Group II. These horses were subjectively evaluated for lameness, pain on palpation, pain with flexion, degree of flexion, swelling and heat before treatment.

In accordance with the invention, all horses of Group I were injected intramuscularly with a one time dose of 500 mg sodium chondroitin sulfate D from shark fin extracts purified according to the invention procedure. The initial injections were followed 96 hours later with a maintenance dosage of 500 mg (intramuscularly). These animals were subjectively evaluated on days 1 and 4 for lameness, pain on palpation, pain with flexion, degree of flexion, swelling and heat after before treatment. The results of the treatment are shown in Table I.

COMPARATIVE EXAMPLE 1

To compare the results of the experiment described above, twenty horses of Group II were injected intramuscularly on days 1 and 4 with 500 mg of Adequan, a product of Luitpold Pharmaceuticals. These animals were subjectively evaluated on days 1 and 4 for lameness, pain on palpation, pain with flexion, degree of flexion, swelling and heat after before treatment. The results of the treatment are shown in Table I.

Table 1: Changes in clinical variables* following treatment with i.m. injections of SCPS** and PSGAG***

treatment	number of horses		
	total	positive response (improvement)	negative response (not improvement)
SCPS	20	18	2
PSGAG	20	3	17

* variables: lameness, pain on palpation, pain with flexion, degree of flexion, swelling and heat)

** SCPS: sodium chondroitin sulfate D = sodium chondroitin polysulfate from shark extract. SCPS has a molecular weight in the range of 18,000 to 104,000 Daltons and is essentially free of endotoxin.

*** PSGAG: Adequan i.m.; a product of Luitpoid Pharmaceuticals, Inc.; polysulfated glycosaminoglycan extracted from bovine tracheal tissue and having a molecular weight of 10,000 - 12,000 daltons (see attached literature).

The results indicate that the composition given in a single injection produce consistent, significant analgesic activity as evidenced by favorable response rate of 82 % when given in the claimed doses.

This example is not intended to limit or restrict the scope of the invention in any way, and should not be construed as providing dosage forms, regimens and methods of administration which must be utilized exclusively to practice the invention.

It has thus been shown that there are provided compositions and methods which achieve the various objects of the invention and which are well adapted to meet the conditions of practical use. Various modifications and equivalents will be apparent to one skilled in the art and may be made in the fractions, methods, and pharmaceutical compositions of the present invention without departing from the spirit and scope thereof, and it is therefore to be understood that the invention is to be limited only by the scope of the appended claims.

CLAIMS:

What is claimed is:

Claim 1. A method for the treatment of pain in mammals including humans, comprising administering to said mammal in need of such treatment an analgesic effective amount of a sodium chondroitin sulfate selected from sodium chondroitin sulfate C, sodium chondroitin sulfate D and mixtures thereof, said effective amount exhibiting collagenase inhibitory activity and angiogenesis inhibitory activity; wherein said sodium chondroitin sulfate is derived from shark fin cartilage, is essentially free of endotoxin and has a molecular weight in the range of about 18,000 to about 100,000 Daltons.

Claim 2. The method of claim 1 wherein said sodium chondroitin sulfate is admixed with sodium chondroitin sulfate D.

Claim 3. The method according to claim 1 wherein said molecular weight is in the range of about 40,000 to about 55,000 Daltons.

Claim 4. The method according to claim 1 wherein said effective amount is in the range of from about 0.5 to about 2 mg per kg of body weight.

Claim 5. The method according to claim 1 wherein said pain is associated with acute inflammation of soft tissue, acute inflammation of hard tissue, chronic inflammation of soft

tissue, chronic inflammation of hard tissue, traumatic inflammatory condition, or non-traumatic inflammatory condition.

Claim 6. The method according to claim 1 wherein said mammal is a horse or a human.

Claim 7. The method according to claim 6 wherein said effective amount is administered parenterally, intramuscularly, or transdermally.

Claim 8. The method according to claim 1 wherein said sodium chondroitin sulfate is admixed with dimethyl sulfoxide in a ratio of from about 1:1 to about 1:15 by weight.

Claim 9. The method according to claim 8 wherein said admixture is administered transdermally.

Claim 10. A method for the treatment of pain in mammals including humans, comprising administering to said mammal in need of such treatment an analgesic effective amount of a mixture consisting essentially of at least 60 wt % of sodium chondroitin sulfate C, sodium chondroitin sulfate D or mixtures thereof derived from shark fin cartilage and up to about 40 wt % of sodium chondroitin sulfate derived from non-shark sources selected from the groups consisting of bovious trachea and bovine nasal septum, said composition being essentially free of endotoxin, and wherein each of said sodium chondroitin sulfate

C derived from shark cartilage and sodium chondroitin sulfates derived from non-shark sources has a molecular weight in the range of about 18,000 to about 100,000 Daltons.

Claim 11. The method according to claim 10 wherein said molecular weight is in the range of about 40,000 to about 55,000 Daltons.

Claim 12. The method according to claim 10 wherein said effective amount is in the range of from about 0.5 to about 2 mg per kg of body weight.

Claim 13. The method according to claim 10 wherein said effective amount is administered parenterally, intramuscularly, or transdermally.

Claim 14. The method according to claim 10 wherein said mixture is further admixed with dimethyl sulfoxide in a ratio of from about 1:1 to about 1:15 by weight.

Claim 15. The method according to claim 14 wherein said admixture is administered transdermally or topically.

Claim 16. The method according to claim 3 wherein said effective amount is in the range of from about 0.5 to about 2 mg per kg of body weight.

Claim 17. The method according to claim 16 wherein said mammal is a horse.

Claim 18. The method according to claim 4 wherein said mammal is a horse.

Claim 19. The method according to claim 11 wherein said effective amount is in the range of from about 0.5 to about 2 mg per kg of body weight.

INTERNATIONAL SEARCH REPORT

PCT/US92/09725

A. CLASSIFICATION OF SUBJECT MATTER

IPC(5) :A61K 9/50
US CL :424/548
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : A61K 9/50

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

STN Specific Components Antiinflammatory

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US, A, 4,473,551 (SCHINITSKY) 25 September 1984, See entire document.	1-19
X Y	N, Chemical Abstracts, Volume 112, no. 11, issued 1990, March 12 (Columbus, Ohio, U.S.A.), SMIRNOVA ET AL., Anti-inflammatory effects of chondroitin sulfate based agents, (VNIITKGP, Moscow, USSR). Khim.-Farm Zh. 1989, 23 (12), 1520-2, Abstract No. 91437+.	1-7 1-19
Y	N, Chemical Abstracts, Volume 98, no. 21, issued 1983, May 23 (Columbus, Ohio, U.S.A.) UKAI ET AL., Anti-inflammatory effect of the various polysacchrides, (Gi fu Coll. Pharm., Gif fu, Japan 502). Oyo Yakuri 1983, 25 (2), 203-7 (Eng.), Abstract No. 172808j.	1-19

[ ] Further documents are listed in the continuation of Box C. [ ] See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be part of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search 17 DECEMBER 1992	Date of mailing of the international search report 14 JAN 1993
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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US92/09725

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	N, Chemical Abstracts, Volume 111, no. 1, issued 1989, July 3 (Columbus, Ohio, U.S.A.), CULLIS-HILL ET AL., Polysaccharide sulfate metal complexes for Anti-inflammatory compositions. (Arthropharm Pty. Ltd.) PCT Int Appl. WO 88 07,060 (C1. C08B37/02), 22 September 1988, AU Appl. 87/951 19 March 1987; 76 pp, Abstract No. 739h.	1-19
Y	N, The Merck Index, 10ed, 1985, monoliths 2194 and 3255.	1-19